Peripheral T-cell Lymphomas

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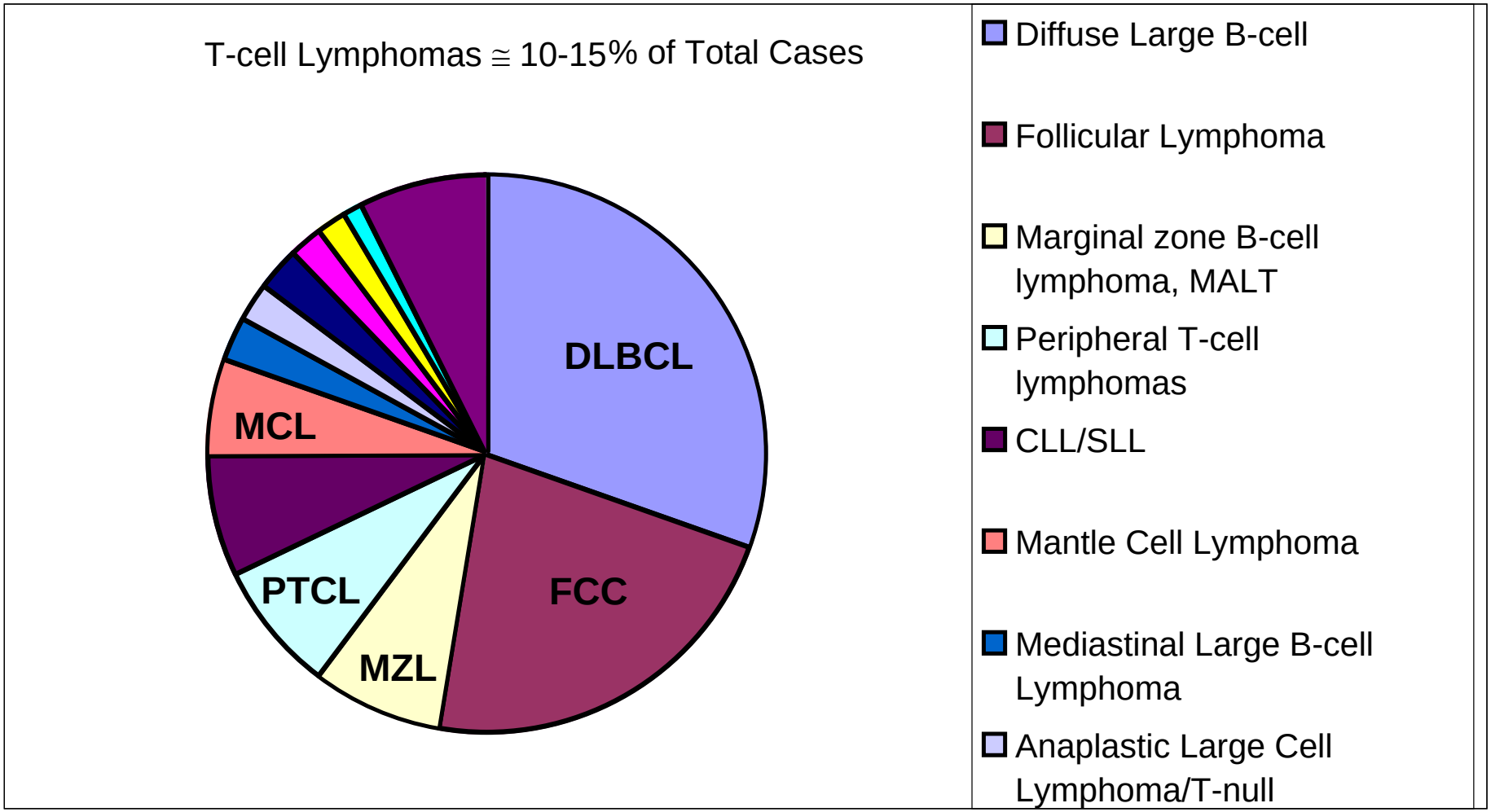
Distribution of Non-Hodgkin's Lymphomas



WHO Classification

Peripheral T-cell lymphoma, US	Nodal
Angioimmunoblastic T-cell lymphoma	
Adult T-cell leukemia/lymphoma (HTLV-1+)	
Anaplastic large cell lymphoma (T & null cell)	
Extranodal NK/Tcell lymphoma, nasal type	Extra-Nodal
Enteropathy-type T-cell lymphomaExtranodal	
Subcutaneous panniculitis-like T-cell lymphoma	
Mycosis fungoides/ Sezary syndrome	Cutaneous
Primary cutaneous CD30+ T-cell LPD	
T-cell prolymphocytic leukemia	Leukemic/ BM
T-cell large granular lymphocytic leukemia	
Aggressive NK-cell leukemia	
Hepatosplenic T-cell lymphoma ($\gamma\delta$)	

Peripheral T & NK Cell Neoplasms

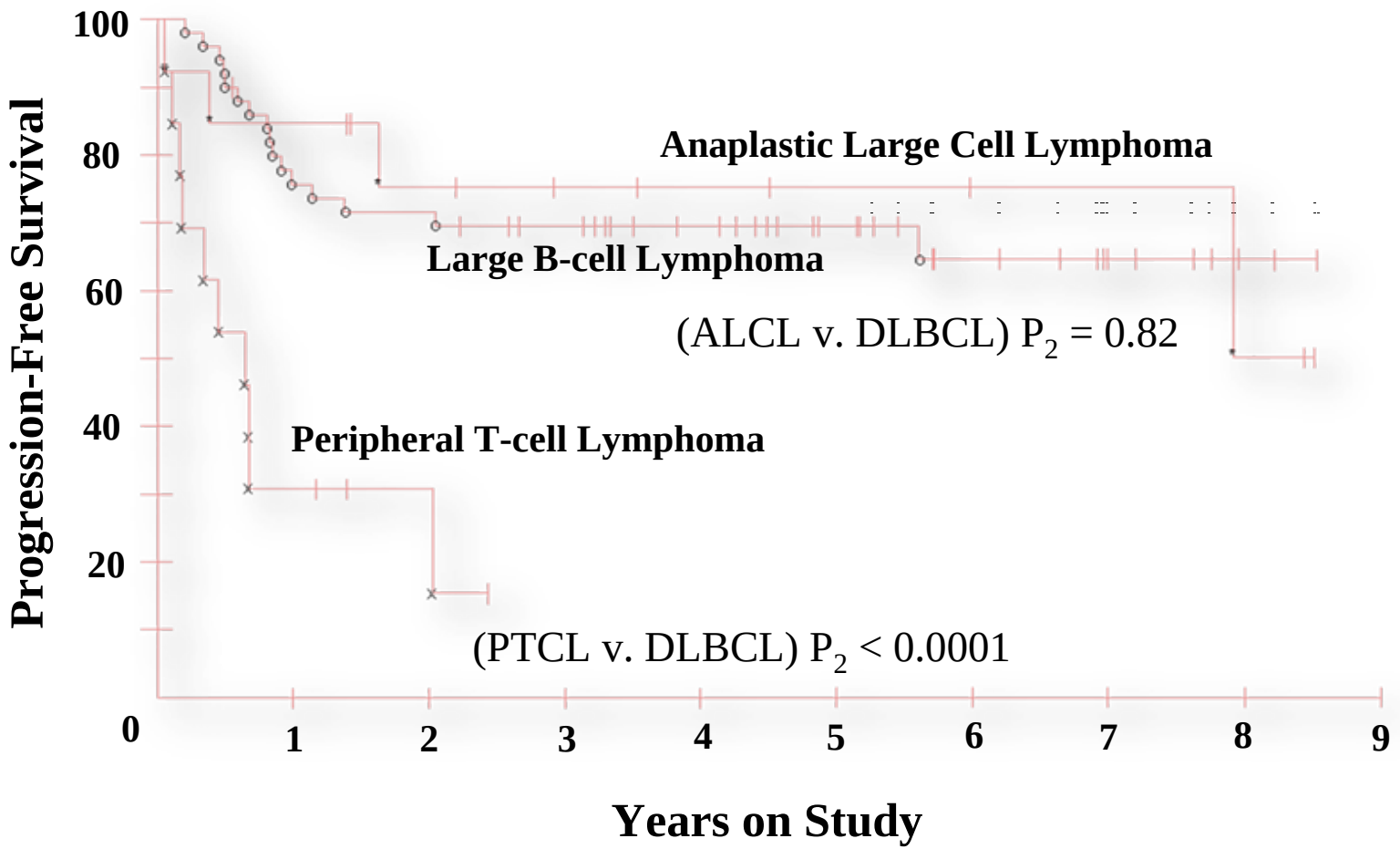
- Infrequent Compared to B-cell Lymphomas
- Molecular pathogenesis unknown for most subtypes
- Most subtypes clinically aggressive and cytological grade is generally not useful
- No standard or curative treatments for most subtypes

Clinical Features of Peripheral T-cell Lymphomas

Generalized lymphadenopathy	50-75%
Skin Involvement	20-50%
Hepatosplenomegaly	25-20%
Liver involvement	10-25%
Bone marrow involvement	25-35%
Hypergammaglobulinemia	25-50%
Stage III/ IV	75%
“B” Symptoms	50-60%

(Based on series from NCI, Nebraska, & Nagoya, Japan)

Initial Doxorubicin-Based Treatment



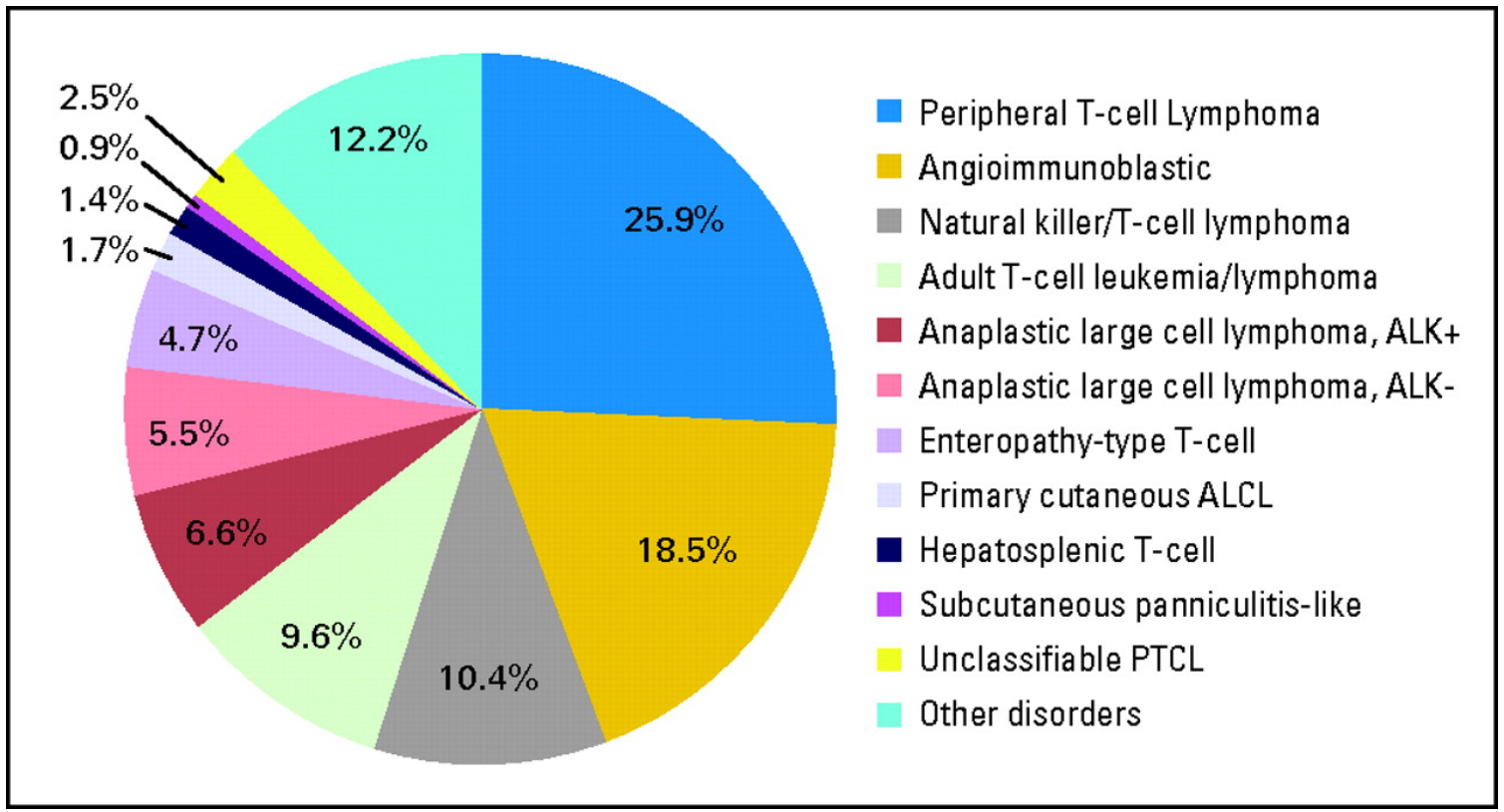
W. Wilson et al

International T-cell NHL Study
Sites (N = 1314)

- **North America**
  - Vancouver, Bethesda (NCI), Nebraska, Massachusetts (MGH), California (USC), Arizona
- **Europe**
  - Barcelona, Norway, Wurzburg, London, Lyon, Leeds, Madrid, Bologna, Modena
- **Asia**
  - Bangkok, Hong Kong, Singapore, Tokyo, Nagoya, Okayama, Fukuoka, Seoul

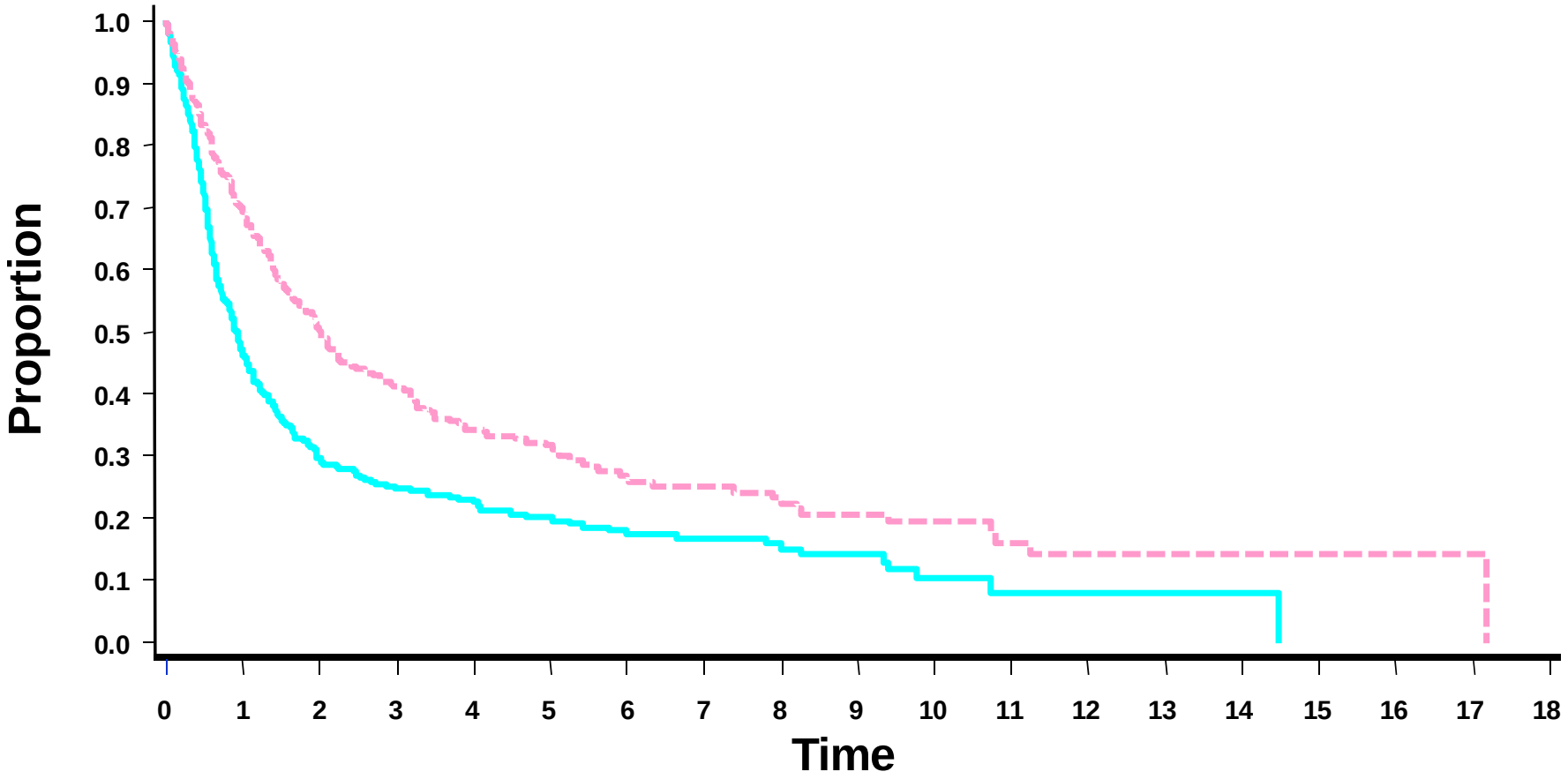
International T-Cell Lymphoma Project

Distribution of 1,314 cases by consensus diagnosis



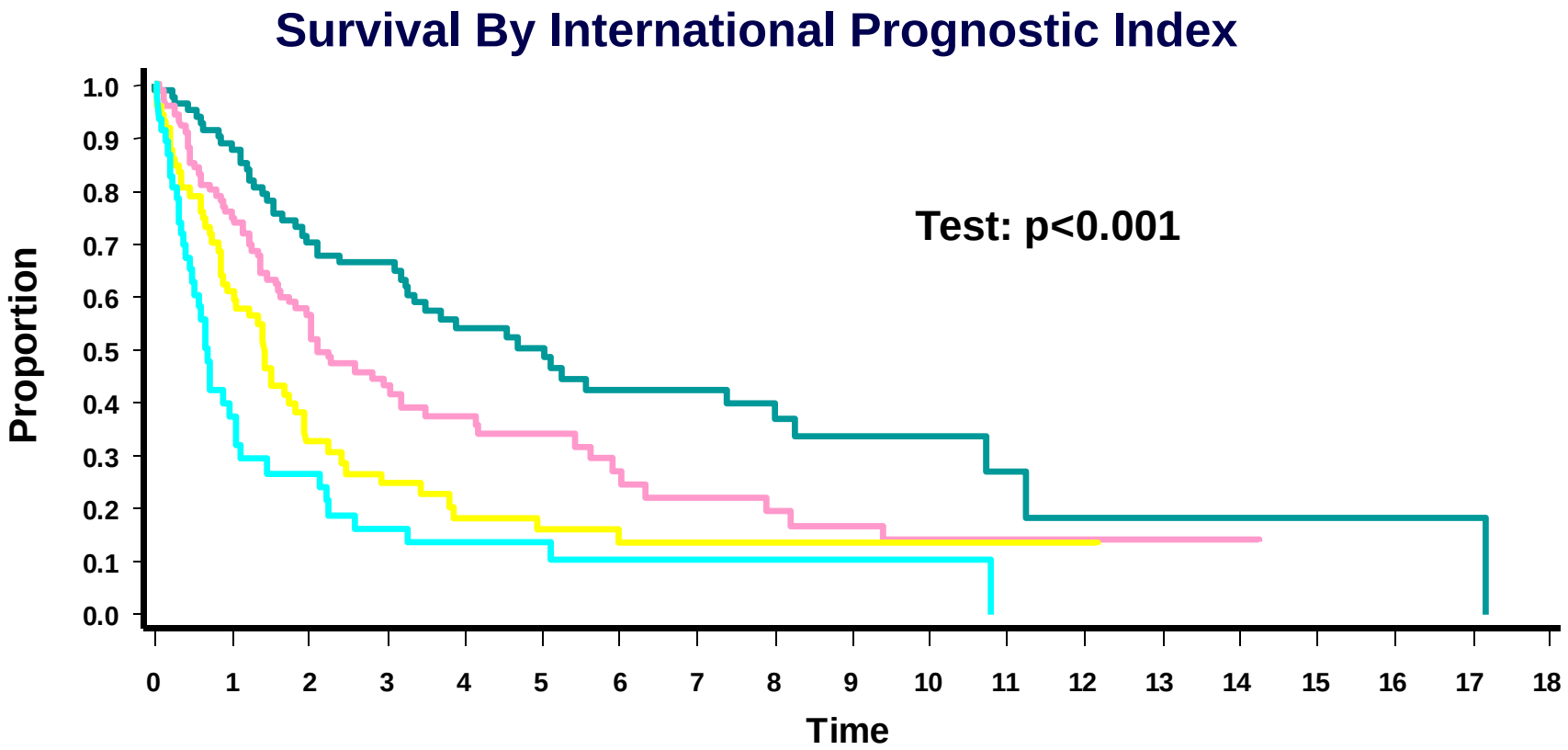
J Clin Oncol; 26:4124-4130 2008

Peripheral T-Cell Lymphomas (NOS)



	CENSOR	FAIL	TOTAL	MEDIAN
FFS	72	261	333	0.91
OAS	112	221	333	2.01

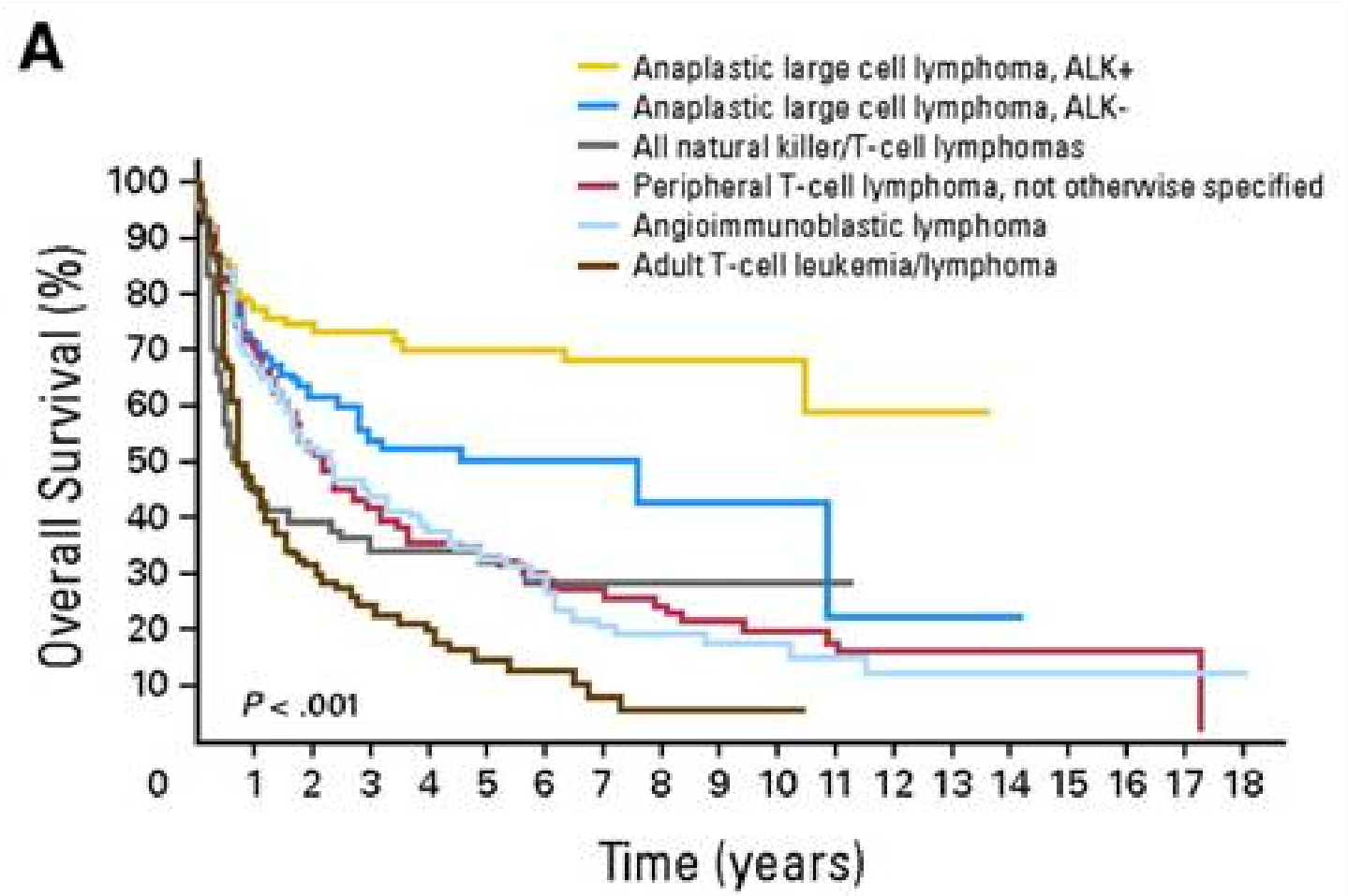
Peripheral T-Cell Lymphomas (NOS)



IPI	CENSOR	FAIL	TOTAL	MEDIAN
0/1	36	47	83	5.03
2	36	67	103	2.1
3	20	53	73	1.41
4/5	9	38	47	0.68

International T-Cell Lymphoma Project

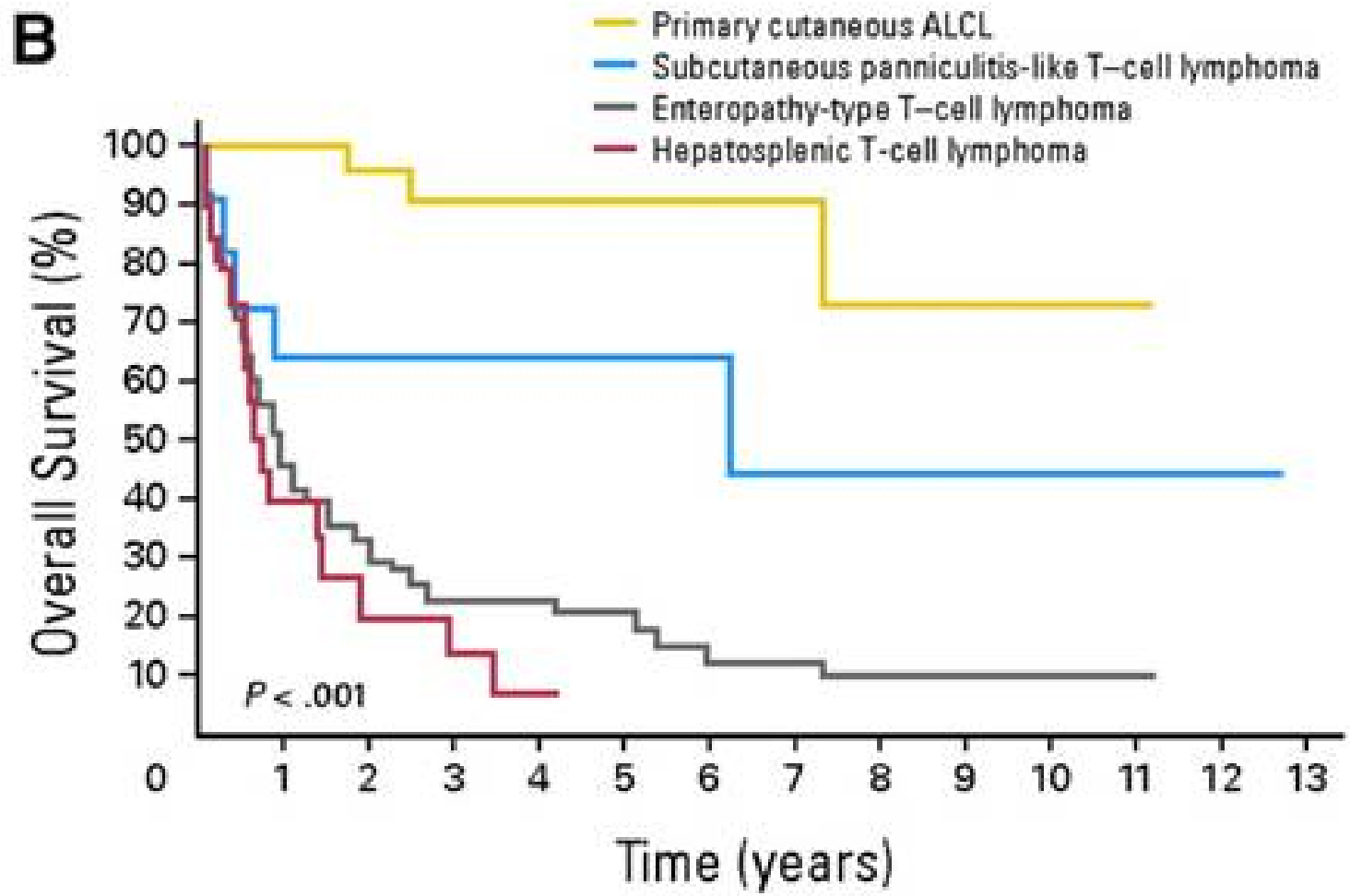
Survival By Subtype of PTCL



J Clin Oncol; 26:4124-4130 2008

International T-Cell Lymphoma Project

Survival By Subtype of PTCL



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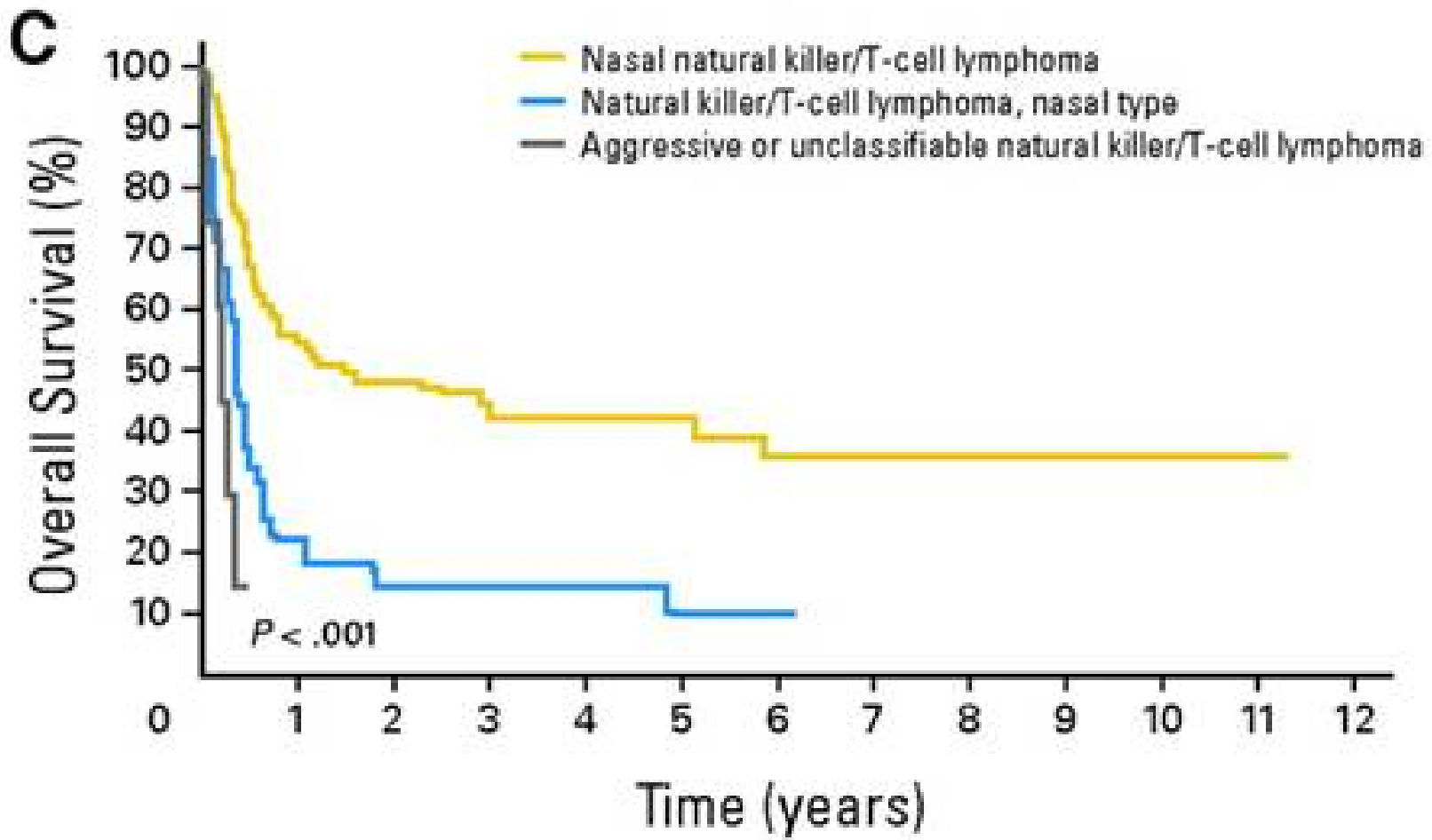
International T-Cell Lymphoma Project

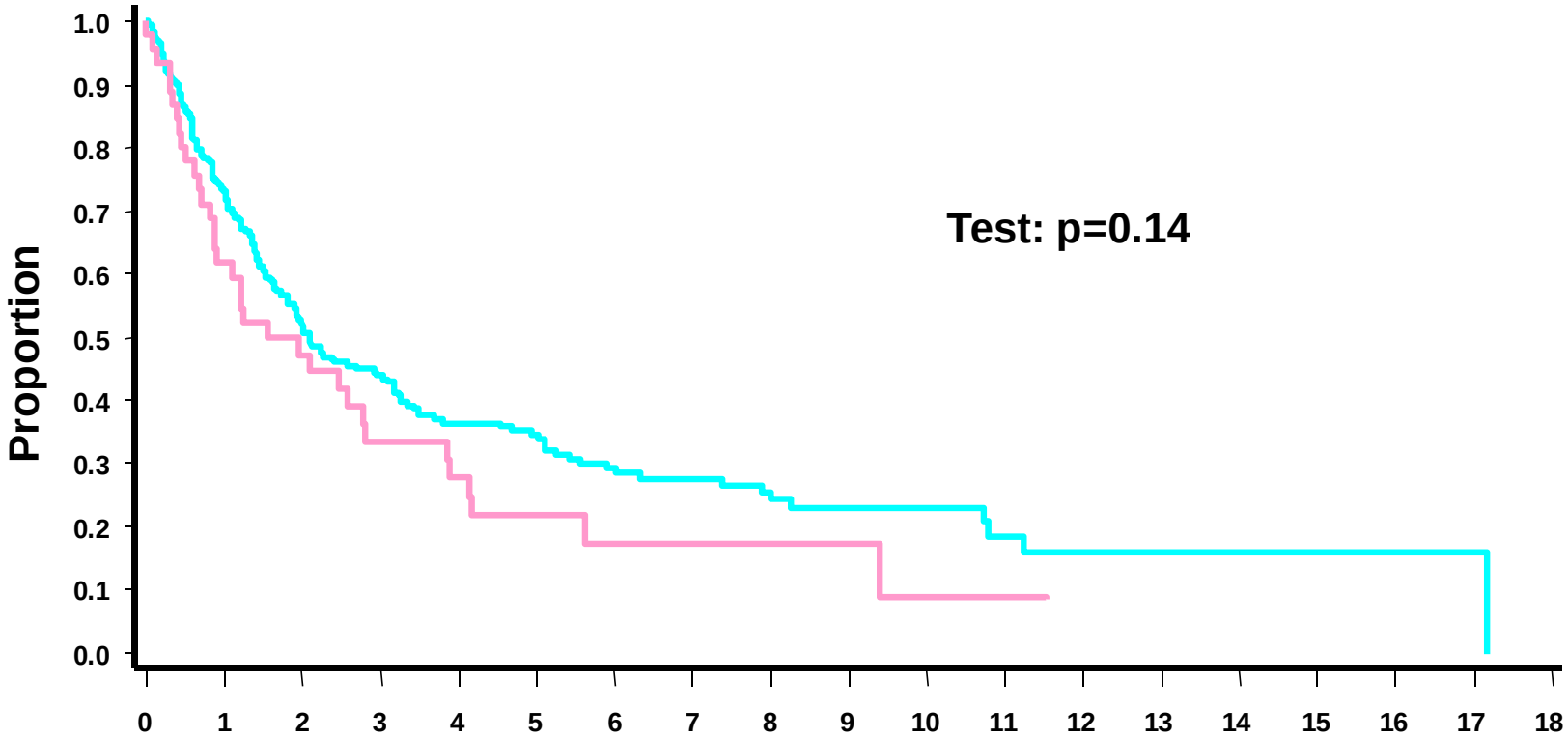
Survival By Subtype of PTCL



J Clin Oncol; 26:4124-4130 2008

International T-Cell Lymphoma Project

Survival By Initial Anthracycline Use

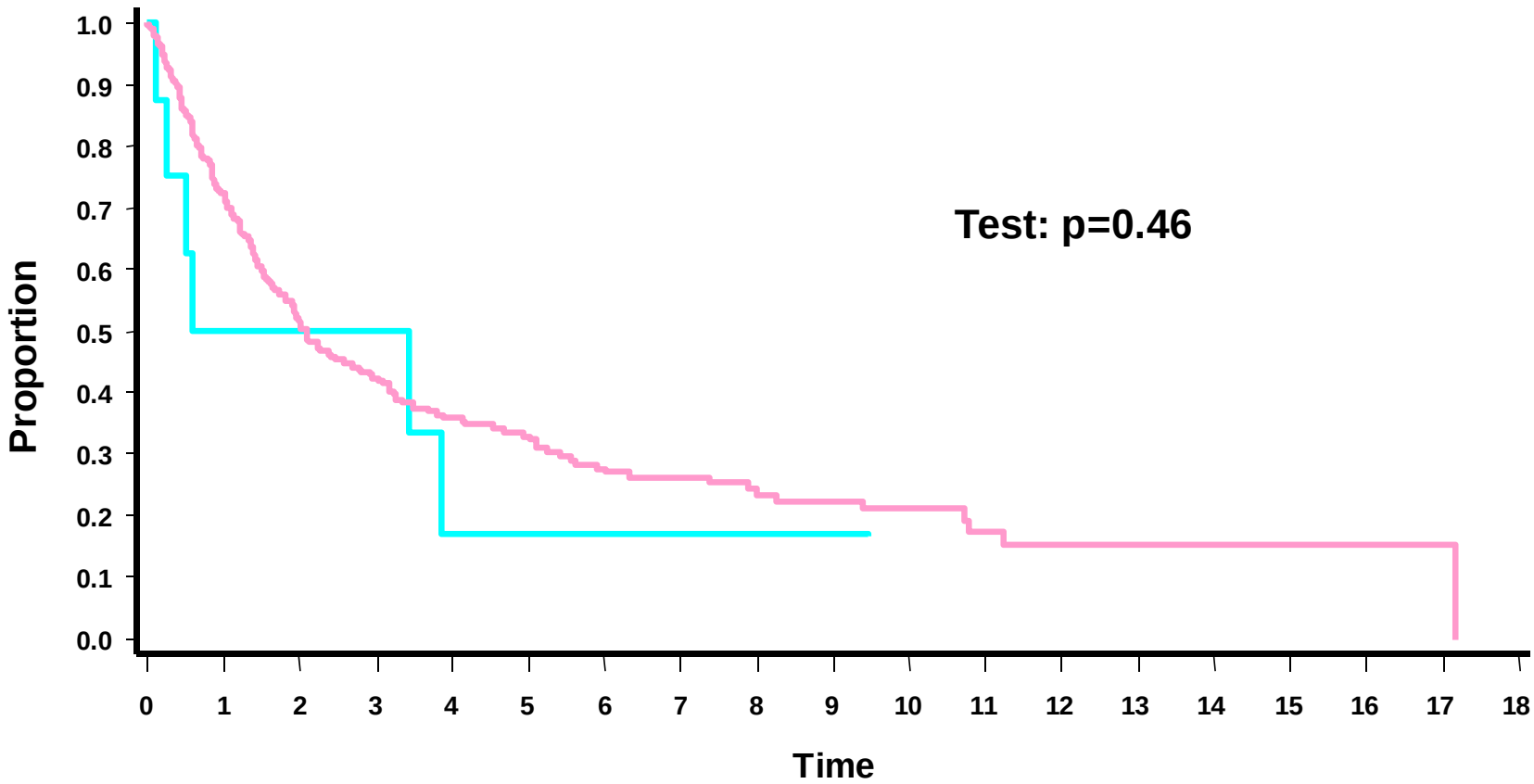


Anthracycline as part of initial tx	CENSOR	FAIL	TOTAL	MEDIAN
yes	98	173	271	2.1
no	14	34	48	1.57

Vose et al

International T-Cell Lymphoma Project

Survival By Initial Platinum Use

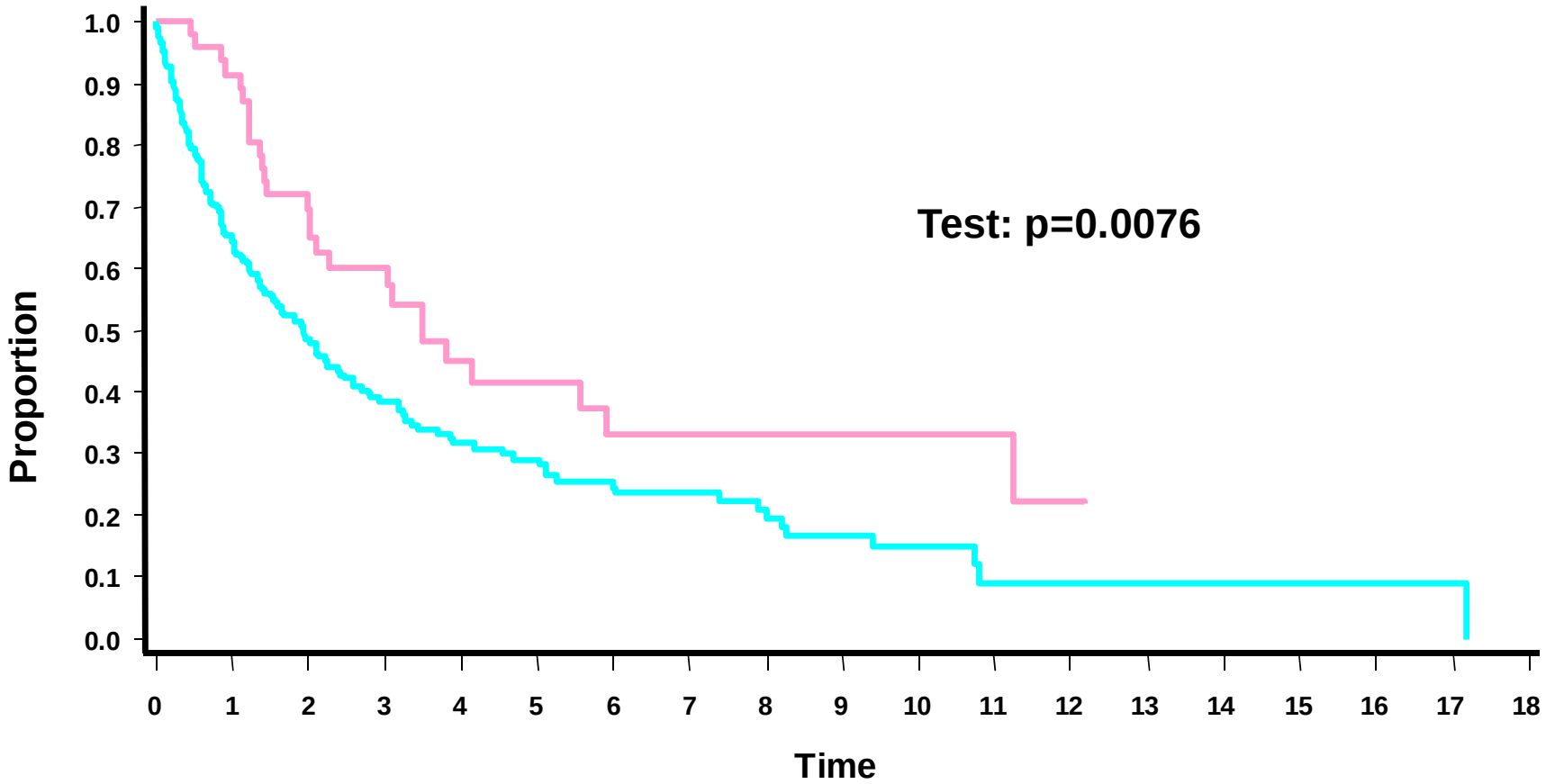


Carbo/Cisplatin as part of initial tx	CENSOR	FAIL	TOTAL	MEDIAN
yes	2	6	8	2.01
no	110	200	310	2.1

Vose et al

International T-Cell Lymphoma Project

Survival By High Dose Treatment (SCT)



Hi-dose therapy (transplant)	CENSOR	FAIL	TOTAL	MEDIAN
yes	21	27	48	3.5
no	63	148	211	1.95

Vose et al

Conclusion

- Peripheral T-cell lymphomas are infrequent
- Need for better molecular understanding
- Most are incurable so there is a need for new agents

- Return to Main

FDA Review of NDA

Folotyn™ (Pralatrexate)

ODAC September 2, 2009

Shakun Malik, MD

NDA 22-468 Review Team

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Project Manager
Milinda Vialpando

NDA 022-468

Proposed indication:

- Pralatrexate as a single agent for the treatment of patients with relapsed or refractory peripheral T-cell lymphoma (PTCL)

Basis for the application:

- Overall Response Rate (ORR) from one single arm pivotal trial (PDX-008)

Outline of Presentation

- Background Information
- Key regulatory history milestones
- Pivotal trial PDX-008
- Major Issues
- FDA review results
  - Efficacy
  - Safety
- Question to ODAC

Pralatrexate

Pralatrexate is a New Molecular Entity (NME) and is a structural analogue of the anti-folate drug methotrexate.

PTCL

- PTCL prevalence is approximately 10-15% of all newly diagnosed NHL.
- The current annual prevalence of PTCL in the U.S. is estimated to be approximately 9,500 patients.

Mature T-cell and NK-cell Neoplasms WHO Classification (2008)

Cutaneous

- Mycosis fungoides
- Sezary syndrome
- Primary cutaneous CD30+ T-cell LPDs
- Primary cutaneous anaplastic LC lymphoma
- Primary cutaneous γδ T-cell lymphoma
- Primary cutaneous CD8+ aggressive epidermotropic lymphoma*
- Primary cutaneous CD4+ small/med T-cell lymphoma*

Leukemic

- T-cell prolymphocytic leukemia
- T-cell large granular lymphocytic leukemia
- Adult T-cell leukemia/lymphoma

Nodal

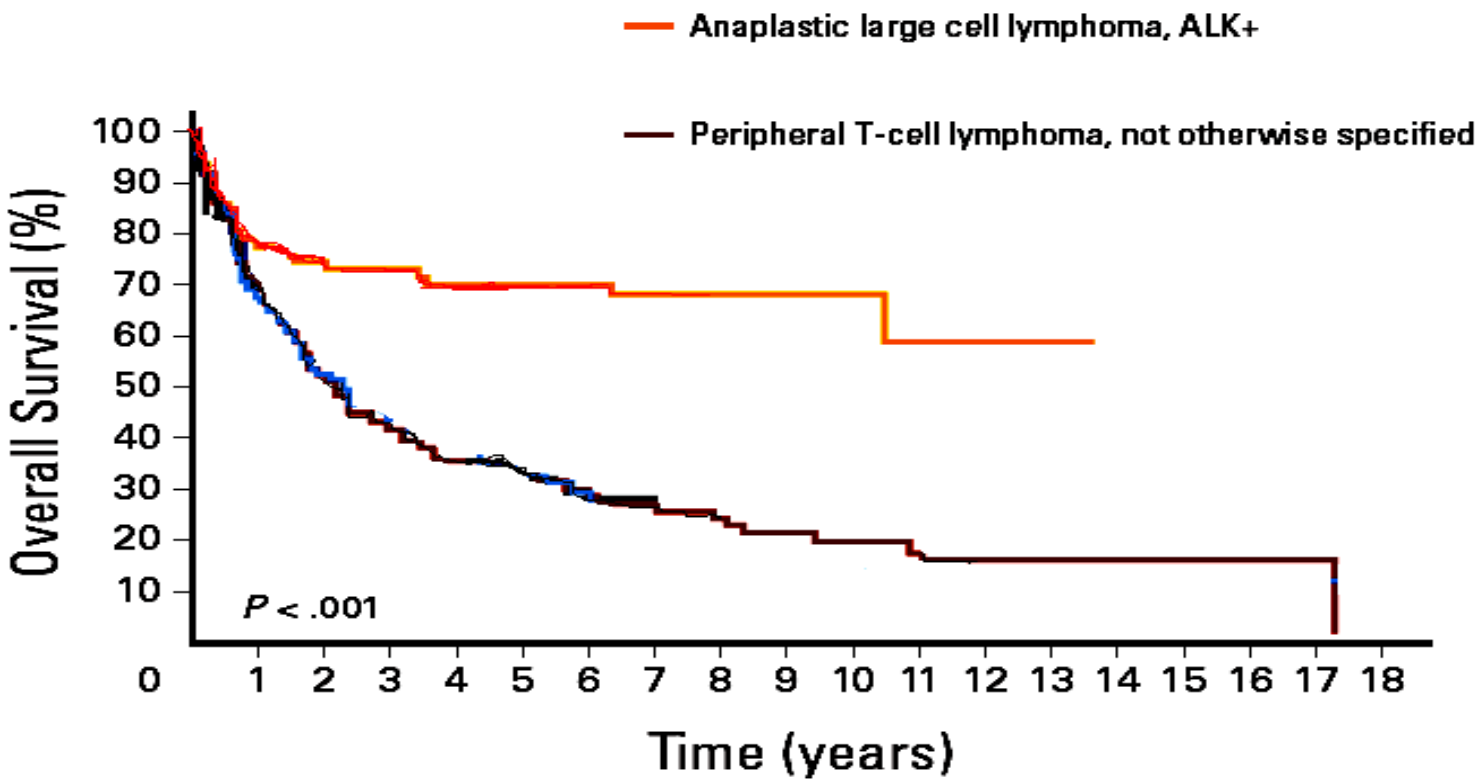
- Angioimmunoblastic T-cell lymphoma
- Anaplastic large-cell lymphoma, ALK pos
- Anaplastic large-cell lymphoma, ALK neg*
- Peripheral T-cell lymphoma, NOS

Extranodal

- Systemic EBV+ T-cell childhood LPD*
- Hydroa vaccineforme-like lymphoma*
- Extranodal NK/T-cell lymphoma, nasal type
- Enteropathy-associated T-cell lymphoma
- Hepatosplenic T-cell lymphoma
- Subcutaneous panniculitis-like T-cell lymphoma

Swerdlow SH et al.: World Health Organization Classification of Tumours of the Haematopoietic and Lymphoid Tissues. IARC Press: Lyon 2008

Overall Survival by PTCL Subtypes



International T-Cell Lymphoma Project, J Clin Oncol; 26:4124-4130 2008

PTCL Treatment

- Currently there are no therapies specifically approved for the treatment of PTCL.
- Randomized trials are lacking.
- Most published series are difficult to interpret partly because of the inclusion of heterogeneous subtypes.

Mechanism	Agent (Reference)	N	ORR (CR) %	Response Duration
Immunotherapy	Denileukin diftitox[17]	27	48 (22)	6 mo
	Denileukin diftitox + CHOP[18]*	31	90 (71)	13 mo
	Alemtuzumab[21]	14	36 (21)	2–12 mo
	Alemtuzumab (reduced dose)[22]	10	60 (20)	7 mo
	Alemtuzumab + CHOP[23]*	24	75 (71)	11 mo
	Zanolimumab[27]	21	24 (9)	1–8 mo
	Siplizumab[28]	9	11 (11)	NR
Antimetabolite	Gemcitabine[31]	13	69 (8)	NR
	Gemcitabine[30]	10	60 (20)	13 mo
	Pentostatin[32]	5	80 (40)	4 mo
	Pralatrexate	16	62 (56)	NR
HDAC	Romidepsin[39]	19	26 (10)	8–14 mo
	Belinostat[40]	11	18 (9)	3–4 mo
AITL-specific	Cyclosporine[52]	12	67 (25)	2–120 mo
	Rituximab + CHOP[53]*	9	89 (89)	7–53 mo
nNK/T-specific	Asparaginase[57]	33	51 (51)	55% OS at 5 y
ALCL-specific	SGN-30[58]	39	20 (5)	1–12 mo
	MDX-060[59]	7	28 (28)	2–24 mo

*Frontline therapy. All other studies in relapsed/refractory. Response duration listed as median if available or range.
Abbreviations: AITL, angioimmunoblastic T-cell lymphoma; ALCL, anaplastic large-cell lymphoma; CHOP, cyclophosphamide, doxorubicin, vincristine, prednisone; CR, complete response rate; HDAC, histone deacetylase; nNK/T, natural killer/T-cell lymphoma; NR, not reported; ORR, overall response rate; OS, overall survival.

PDX-008 (PROPEL) Study

A Multi-center, Phase 2, Open-label Study of (RS)-10-Propargyl-10-Deazaaminopterin (Pralatrexate) with Vitamin B12 and Folic Acid Supplementation in Patients with Relapsed or Refractory Peripheral T-cell Lymphoma

Main Concerns with this NDA

- Duration of Response
  - ORR of 27% (95% CI: 19-36)
  - Only 12% of patients had a duration of response ≥14 weeks
  - Duration of response ≤14 weeks in 55% of responders
- Responses adjudicated in 52% of the responders
- Inherent problems with single arm studies

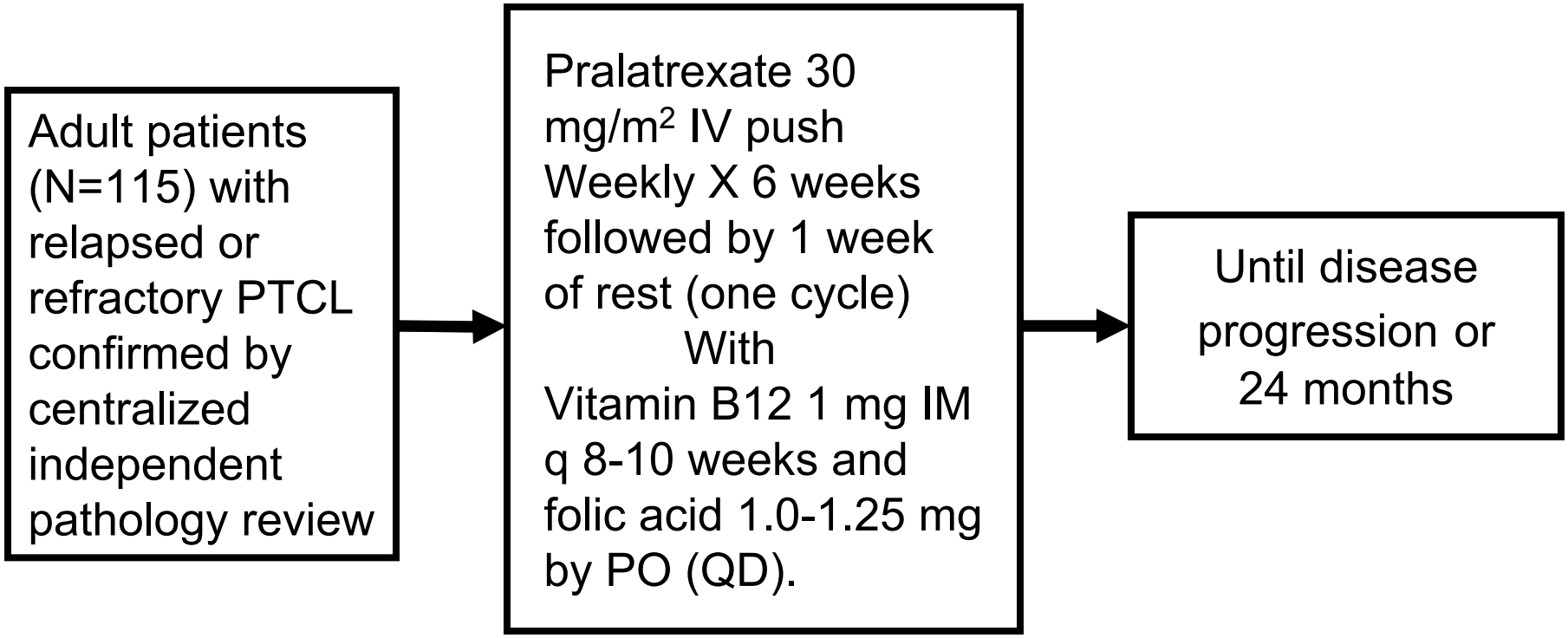
Key Regulatory History Milestones

- February 6, 2006: End of Phase I/II meeting
- July 20, 2006: Orphan-product designation
- Sept 28, 2006: Fast track designation
- July 28, 2006: Special Protocol Assessment (SPA)

SPA Agreement

FDA agreed that the primary endpoint of ORR is acceptable; **however, the magnitude and duration of response for approval would be a review issue.**

PDX-008 Trial Design



PDX-008 Key Eligibility Criteria

- Histologically/cytologically confirmed PTCL by central pathological review
- Clear documented progressive disease after at least 1 prior treatment
- At least 1 biopsy from the initial diagnosis or in the relapsed setting to confirm the diagnosis of PTCL

PDX-008 Key Eligibility Criteria

- No restriction on maximum number of prior therapies
- ECOG PS 0 – 2
- Adequate hematological, hepatic, and renal function
  - Platelets ≥ 100,000/μL
  - ANC ≥ 1,000/μL
  - Bilirubin ≤ 1.5 mg/dL
  - ALT/AST ≤ 2.5 x ULN
  - Creatinine ≤ 1.5 mg/dL

Eligible Histological Subtypes

- T/Natural killer (NK) cell leukemia/lymphoma
- Adult T-cell leukemia/lymphoma (human T-cell leukemia virus [HTLV] 1+)
- Angioimmunoblastic T-cell lymphoma
- Blastic NK lymphoma (with skin, lymph node, or visceral involvement)
- Anaplastic large cell lymphoma, primary systemic type
- PTCL – unspecified
- T/NK-cell lymphoma – nasal
- Enteropathy-type intestinal lymphoma
- Hepatosplenic T-cell lymphoma
- Extranodal peripheral T/NK-cell lymphoma – unspecified
- Subcutaneous panniculitis T-cell lymphoma
- Transformed mycosis fungoides

Endpoints

- **Primary Endpoint**:
  - Response rate (CR + CRu + PR) according to IWC assessed by independent central review
- **Secondary Endpoints:**
  - Duration of response
  - Progression-free survival
  - Overall survival

According to IWC

- No requirement for confirmatory scans for response

Report of an International Workshop to Standardize Response Criteria for Non-Hodgkin's Lymphomas

Bruce D. Cheson, Sandra J. Horning, Bertrand Coiffier, Margaret A. Shipp, Richard I. Fisher, Joseph M. Connors,

J Clin Oncol 17:1244-1253, 1999

IWC Response Criteria for NHL

Response Category	Physical Examination	Lymph Nodes	Lymph Node Masses	Bone Marrow
CR	Normal	Normal	Normal	Normal
CRu	Normal	Normal	Normal	Indeterminate
	Normal	Normal	> 75% decrease	Normal or indeterminate
PR	Normal	Normal	Normal	Positive
	Normal	≥ 50% decrease	≥ 50% decrease	Irrelevant
	Decrease in liver/spleen	≥ 50% decrease	≥ 50% decrease	Irrelevant
Relapse/progression	Enlarging liver/spleen; new sites	New or increased	New or increased	Reappearance

"**Response rates** do not necessarily influence other measures of overall clinical benefit or outcome in patients with lymphoma. **Durable complete responses**, if associated with measures of clinical benefit, may be relevant."

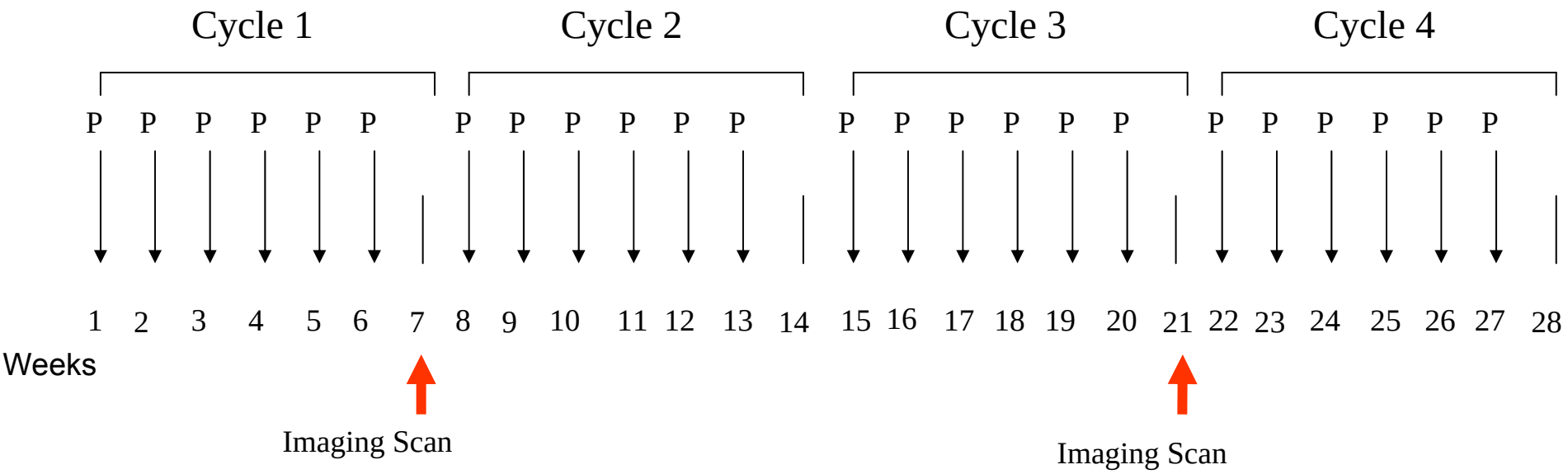
VOLUME 25 · NUMBER 5 · FEBRUARY 10 2007
JOURNAL OF CLINICAL ONCOLOGY
SPECIAL ARTICLE

Revised Response Criteria for Malignant Lymphoma

Primary Endpoint Evaluations

- Clinical evaluation
- Bone marrow biopsy
- Imaging modality
  - CT or MRI
  - Medical photography with ruler measurement of cutaneous lesions
  - PET scans

Treatment Schedule and Evaluation Schema



- Cycles repeat until disease progression or condition met as described in section 6.3
- After cycle 1, scans every 14 weeks just prior to the first dose of an even cycle
- P = pralatrexate

PDX-008 Results

Patient Population

115 Patients enrolled

- 80 (69%) US
- 26 (23%) Europe
- 9 (8%) Canada
- Safety analyses on 111 patients
  - 4 patients did not receive pralatrexate
- Efficacy analyses on 109 evaluable patients
  - 2 treated patients did not have eligible histology per central pathology review

Central Pathology Confirmation

- 109 evaluable patients
- 86/115 (77%) from previous tissue blocks
- 25/115 (22%) from tumor re-biopsy
- 3/109 (3%) needed clinical assessment by the PI to help make pathological diagnosis after retrospective review of patient records

Patient Characteristics

Category	Parameter	Pralatrexate Treated (N = 111)	
		N	Percent
Gender	M	76	68
	F	35	32
Race	White	80	72
Age (years)	≤ 65	71	64
	≥ 65	40	36
ECOG PS	0	43	39
	1	49	44
	2	19	17

Histology

Histopathology	Per Independent Central Review (N = 111)	
	N	Percent
PTCL-unspecified	59	53
Anaplastic large cell lymphoma, primary systemic	17	15
Angioimmunoblastic T-cell lymphoma	13	12
Transformed mycosis fungoides	12	11
Blastic NK lymphoma (with skin, lymph node, or visceral involvement)*	4	4
T/NK-cell lymphoma-nasal*	2	2
Extranodal peripheral T/NK-cell lymphoma unspecified*	1	< 1
Adult T-cell leukemia/lymphoma (HTLV 1+)	1	< 1
Mycosis fungoides (not transformed)	1	< 1
Inconsistent with T-cell lymphoma	1	< 1

Prior Therapies

Prior Regimen	N	Percent
1	23	21
2	30	27
3	23	21
4	14	13
≥5	21	19
Median (range)	3.0 (1-12)	

PDX-008 Efficacy Results

Main Concerns with this NDA

- Duration of response
  - ORR of 27% (95% CI: 19-36)
  - Only 12% of patients had a duration of response ≥14 weeks
  - Duration of response ≤14 weeks in 55% of responders
- Responses adjudicated in 52% of the responders
- Inherent problems with single arm studies

PDX-008 Efficacy Results

	Central Review N = 109
CR+CRu+PR 95% CI	29 (27%) 19-36%
CR	7 (6%)
CRu	2 (2%)
PR	20 (18%)

FDA Analysis of PDX-008 Trial Data

- After review of the data submitted, the FDA agrees that 29/109 evaluable patients had a response seen on a scan.
- Only 13/29 of these responders maintained duration of that response for ≥14 weeks (time interval between scans).

FDA Analysis of PDX-008 Response Results

	N=109	%
Responses ≥ 14 weeks CR+CRu+PR 95 % CI	13	12 7-20
CR	6	6
CRu	1	1
PR	6	6

Duration of Response

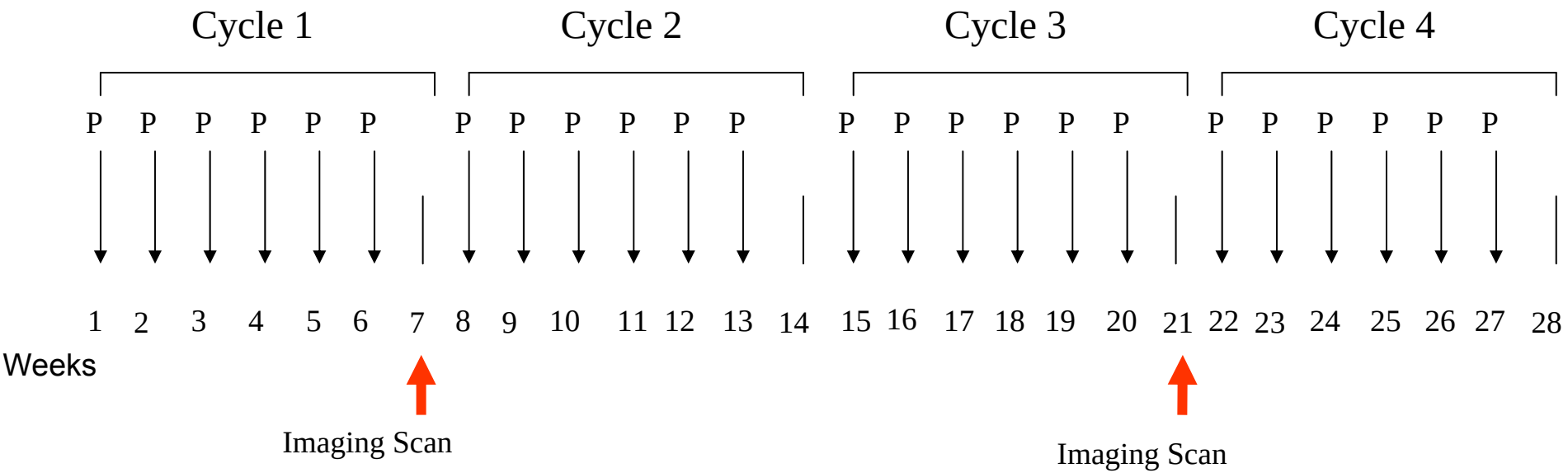
Patients were designated as responders when their nodal shrinkage met the IWC criteria on a given scan.

Response Evaluations

Tumor status of all patients enrolled was evaluated by imaging scans. Target lesions at baseline were:

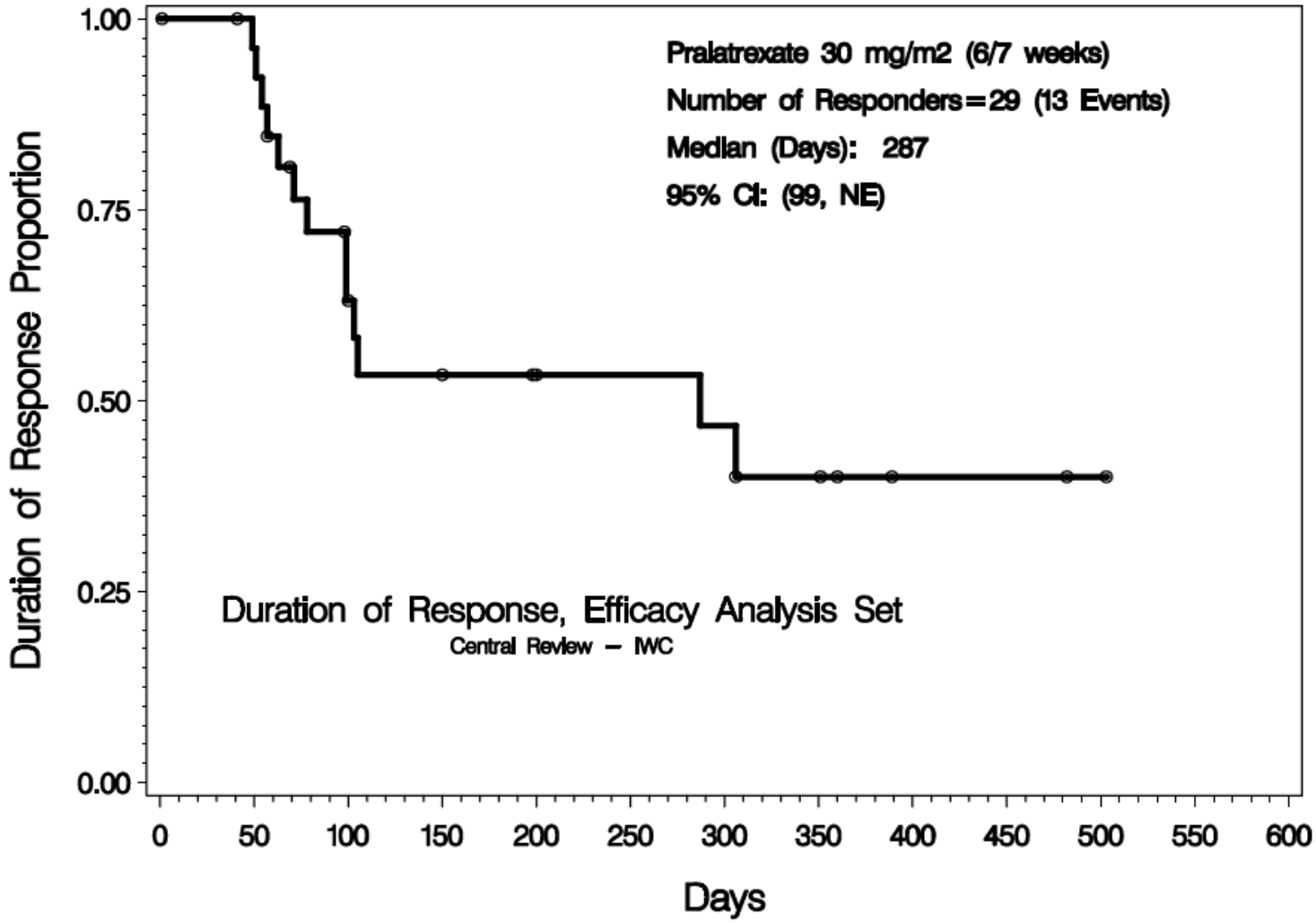
- 1 (1%) Cutaneous only
- 92 (84%) Radiology only
- 15 (14%) Both

Evaluation Schema

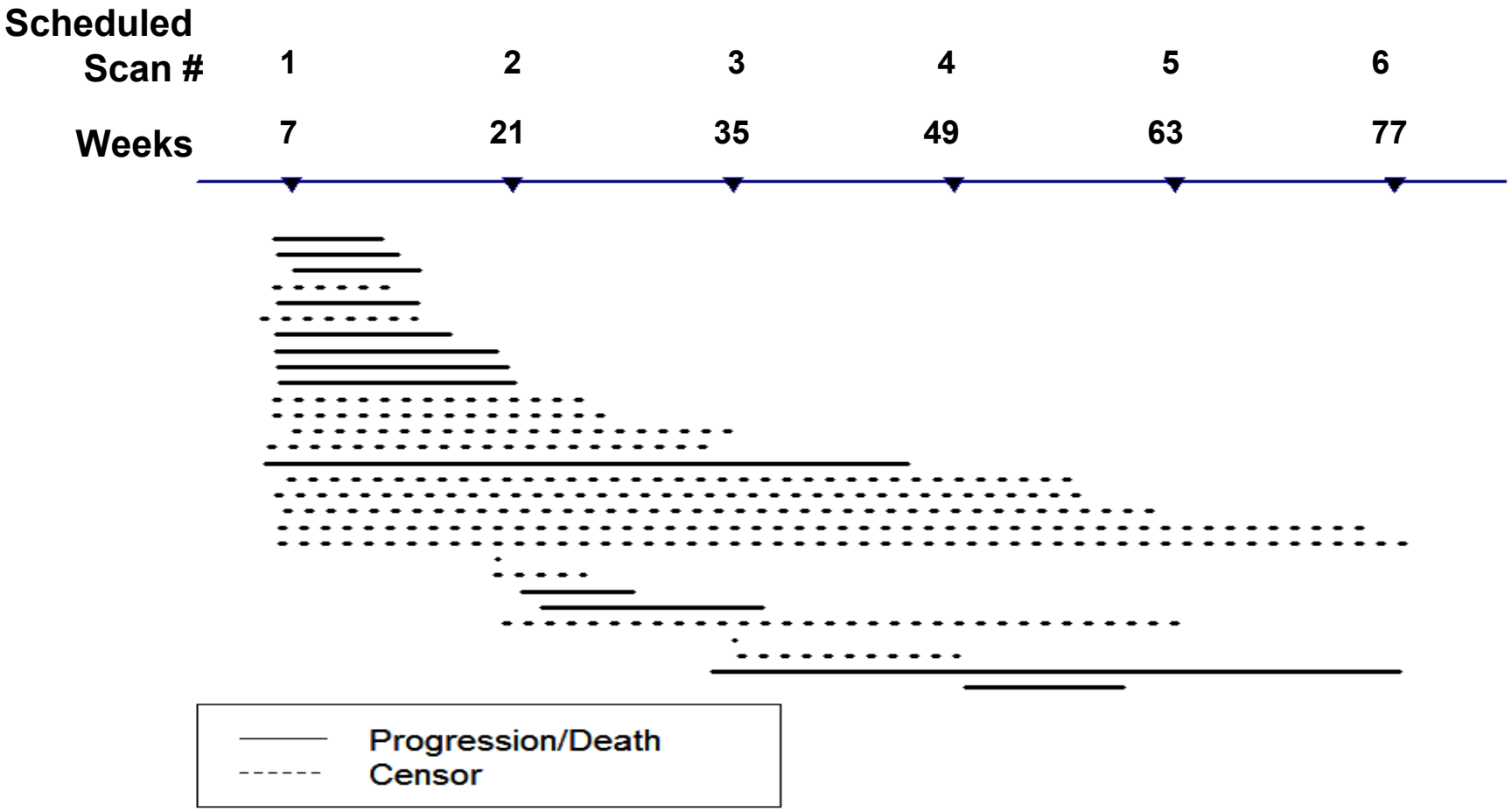


- Cycles repeat until disease progression or condition met as described in section 6.3
- After cycle 1, scans every 14 weeks just prior to the first dose of an even cycle
- P = pralatrexate

Applicant's Kaplan-Meier Estimate of Duration of Response



Analysis of Duration of Response for Individual Responders



Duration of Response

16/29 (55%) responders had a duration of response that was less than 14 weeks (time between 2 consecutive scans).

- 10/16 responders did not maintain response on subsequent scan.
- 3/16 responders had no subsequent imaging scans due to off-study treatment
  - 2 went off due to consent withdrawal and
  - 1 due to SAE that resulted in death.
- 3/16 responders were censored
  - 2 because of BMT and
  - 1 at the study cut off date.

High Adjudication Rate for Responders

Responses in 15 of 29 (52%) responders were adjudicated due to the disagreement between central reader 1 and 2 of the independent imaging review committee.

Confounding Factors Affecting Response

- Radiation to only site of disease prior to study enrollment
- Waxing and waning of nodes without any treatment in lymphomas
- Medications (anti-inflammatory and or corticosteroids)
- Infections and inflammations

FDA Analysis of PDX-008 Response Results

	N=109	%
Responses ≥ 14 weeks CR+CRu+PR 95 % CI	13	12 7-20
CR	6	6
CRu	1	1
PR	6	6

Summary of 6 CRs and 1 CRu with DOR ≥ 14 Weeks

	Previous Therapy	Histological Subtype	Response to Pralatrexate Adjudicated
CR 6	3 pts ≥ 3 2 pts ≥ 2 1 pt ≥ 1	2 pts: ALCL 1 pt: T/NK cell 3 pts: PTCL (NOS)	CR in 5 of 6 patients were adjudicated
CRu 1	4	PTCL (NOS)	Yes

Summary of Efficacy

- Duration of response < 14 weeks in 55% of responders
- High adjudication rate (52%) and confounding factors

Subsequent Therapy for PTCL after Pralatrexate Treatment

	Subsequent Therapy	Efficacy Analysis Set (N=109) n (%)
Initial Subsequent Treatment for PTCL	**Non platinum-containing multi-agent chemotherapy**	**19 (17)**
	Platinum-containing multi-agent chemotherapy	**14 (13)**
	Single-agent chemotherapy	**14 (13)**
	Systemic investigational agents	**8 (7)**
	Radiation therapy with or without systemic treatment	**4 (4)**
	Steroids alone	**4 (4)**
	CHOP	**2 (2)**
	Other	**2 (2)**
	Bexarotene	**1 (<1)**
	Denileukin diftitox	**1 (<1)**
Subsequent Stem Cell Transplant at Any Time		**13 (12)**

Safety

Safety assessments were performed on 111 enrolled patients who had received at least one dose of pralatrexate.

- Adverse Events (AEs)
- Serious Adverse Events (SAEs)
- Death

AEs

- All patients on the trial reported at least 1 AE that was thought to be drug related.
- Mucositis and thrombocytopenia were the commonest AEs.
- AEs were the reason for
  - Dose reductions: 31%
  - Dose omission: 69%
  - Treatment withdrawal: 23%

AEs Occurring in ≥ 20% of Patients (N = 111)

Adverse Event	Grade 1	Grade 2	Grade 3	Grade 4	Total
Mucosal inflammation	**20%**	**30%**	**17%**	**4%**	**70%**
Thrombocytopenia	**1%**	**7%**	**14%**	**19%**	**41%**
Nausea	**24%**	**12%**	**4%**	**--**	**40%**
Fatigue	**19%**	**11%**	**5%**	**2%**	**36%**
Anemia	4%	14%	15%	2%	34%
Constipation	24%	9%	--	--	33%
Pyrexia	23%	8%	1%	1%	32%
Edema	18%	11%	1%	--	30%
Cough	23%	4%	1%	--	28%
Epistaxis	24%	2%	--	--	26%
Vomiting	16%	7%	2%	--	25%
Neutropenia	**--**	**5%**	**13%**	**7%**	**25%**
Diarrhea	13%	6%	2%	--	21%

Grade 3 and 4 AEs

Adverse Event	Grade 3/4
Mucosal inflammation	21%
Thrombocytopenia	33%
Neutropenia	20%

Serious Adverse Events

The total number of SAEs reported are 107 in 49 patients.

The SAEs reported for > 3 patients included

- Pyrexia 8
- Mucosal Inflammation 6
- Febrile Neutropenia 5
- Sepsis 5
- Thrombocytopenia 3

Early Deaths

8 deaths within 30 days of their last dose of pralatrexate

- 7 were attributed to PD
- 1 to cardiopulmonary arrest (possibly related to pralatrexate)

Reasons for Treatment Discontinuation

Patients who discontinued study treatment	102 (92%)
Reason for discontinuing study treatment	
Disease Progression	64 (58%)
Adverse Event	25 (23%)
Investigator Decision	7 (6%)
Patient Decision	5 (5%)
Other	1 (< 1%)

Drug Exposure

- 45/109 (41%) Off before cycle 2 or 8 weeks
- 85/109 (78%) Off before cycle 4 or 21 weeks (64% due to PD)

Conclusion of PDX-008 trial

- ORR of 27% (95% CI: 19-36)
  - **7 CR and 2 CRu**
- Only 12% of patients had a duration of response ≥ 14 weeks.
  - **6 CR and 1 CRu (2 ALCL, 1 NK cell lymphoma and 4 with PTCL-NOS)**
  - **Duration of response < 14 weeks in 55% of responders**
- High adjudication rate (52%) and confounding factors
- 70% of patients received subsequent therapies after pralatrexate
- Most common Grade 3 and 4 toxicities were thrombocytopenia, mucositis and neutropenia.

ODAC Question (Voting)

This NDA submission is based on an overall response rate from a single arm trial using pralatrexate as a single agent in the treatment of 109 patients with relapsed or refractory PTCL. Tumor status was assessed by imaging scans performed at week 7 after initiation of pralatrexate treatment and subsequently every 14 weeks. The responses were evaluated by an independent imaging review committee (IRC).

- **The applicant reported an overall response rate of 27% (95% CI: 19-36%) according to the International Workshop Criteria (IWC) for malignant lymphoma.**
- **Response determination was adjudicated in 52% of responders because of the disagreement between central readers 1 and 2 of the IRC.**
- **Due to the absence of confirmatory scans for responders after initial response designation according to IWC, the duration of response (DOR) in 55% of responders was found to be < 14 weeks. Only 12% of 109 evaluable patients (13 responders) had a DOR ≥ 14 weeks. Nine of these 13 responders (69%) had their response determination adjudicated.**
- **Seventy percent of patients received subsequent therapies after pralatrexate treatment.**
- **The most common grade 3 and 4 toxicities were thrombocytopenia, mucositis and neutropenia.**
- **The applicant has no on-going phase 3 clinical trials for pralatrexate in any indication.**

Question to ODAC

VOTE: As noted above, the Applicant has provided a single arm trial with an overall response rate of 27%. The majority of these responses were partial responses (18%) and only 8% were CR or CRu. The duration of response was less than 14 weeks in 55% of responders. **Are the response rate and duration of response results "reasonably likely" to predict for clinical benefit?** Clinical benefit in lymphomas would be defined as an improvement in overall survival or a robust effect on progression-free survival. Please discuss in your answer the importance of partial responses in predicting clinical benefit as defined above.

- Return to Main

BACKUP – SLIDE

FDA's Evaluation of Responses

Pt #	Status	Best Response	Status	Type	Duration(days)
26	Off	PR	Event	PD	**306**
64	Off	PR	Event	PD	**287**
59	Off	CR	Censored	Transplant	**150**
67	Off	CR	Censored	Transplant	**100**
49	Off	PR	Censored	Transplant	69
10	Off	CR	Censored	Transplant	41
29	Off	CR	Censored	Other Therapy	**306**
92	Off	PR	Censored	Study Term	57
35	On	CRu	Censored	Continuing	**503**
36	On	CR	Censored	Continuing	**482**
57	On	PR	Censored	Continuing	**389**
52	On	CR	Censored	Continuing	**360**
41	Off	CR	Censored	Continuing	**351**
113	On	PR	Censored	Continuing	**200**
105	On	PR	Censored	Continuing	**198**
86	On	PR	Censored	Continuing	**98**